UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,418	02/04/2004	Herve Le Mouellic	03495.0362-09000	1932

22852 7590 03/16/2010

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
03/16/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,418	LE MOUELLIC ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/04/2010 has been entered.

Claims 71, 76 and 77 are amended. Claims 71-77 are pending and currently under examination.

This application 10/770,418 filed on Feb. 04, 2004 is a CON of 10/639,754 08/13/2003 which is a CON of 08/466,699 06/06/1995 PAT 6,638,768, which is a CON of 08/301,037 09/06/1994 PAT 6,528,313, which is a CON of 08/048,056 04/19/1993 ABN, which is a CON of 07/598,679 12/19/1990 ABN. Relevant foreign applications are FRANCE PCT/FR90/00185 03/19/1990 and FRANCE 89 03630 filed on 03/20/1989.

Priority

This application 10/770,418 filed on Feb. 04, 2004 is a CON of 10/639,754 08/13/2003 which is a CON of 08/466,699 06/06/1995 PAT 6,638,768, which is a CON of 08/301,037 09/06/1994 PAT 6,528,313, which is a CON of 08/048,056 04/19/1993 ABN, which is a CON of 07/598,679 12/19/1990 ABN. Relevant foreign applications are FRANCE PCT/FR90/00185 filed on 03/19/1990 and FRANCE 89 03630 filed on 03/20/1989.

It is noted that, the FRANCE PCT/FR90/00185 03/19/1990 and FRANCE 89 03630 filed on 03/20/1989 are not written in English, and there is no support can be found in FRANCE PCT/FR90/00185 03/19/1990 and FRANCE 89 03630 filed on 03/20/1989 for the claims 71-76

filed on 01/05/2010. Therefore, in the absence of a certified translation of FRANCE PCT/FR90/00185 03/19/1990 and FRANCE 89 03630 filed on 03/20/1989 delineating all the limitations recited in claims 71-77 filed on 01/05/2010, the effective filing date for the instant claims is the filing date of 07/598,679 on 12/19/1990.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Previous rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Petkovich et al.** (Petkovich et al., A human retinoic acid receptor which

belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987), is ***withdrawn*** because the claims have been amended and the amended claim 71 recites the limitation "a first gene product that is a receptor".

2. Previous rejection of claim 76 under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Chernajovsky et al.** (Chernajovsky et al., Efficient constitutive production of human fibroblast interferon by hamster cells transformed with the IFN-beta 1 gene fused to an SV40 early promoter. *DNA* 3(4): 297-308, 1984), is ***withdrawn*** because the claims have been amended and the amended claim 76 recites the limitation "a first gene product that is an interferon".

3. Previous rejection of claim 77 under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Lindenmaier et al.** (Lindenmaier et al., Isolation of a functional human interleukin 2 gene from a cosmid library by recombination in vivo. *Gene* 39(1): 33-9, 1985), is ***withdrawn*** because the claims have been amended and the amended claim 77 recites the limitation "a first gene product that is an interleukin".

4. Previous rejection of claims 71 and 74 under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal

beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **George et al.** (George et al., Receptor density and cAMP accumulation: analysis in CHO cells exhibiting stable expression of a cDNA that encodes the beta 2-adrenergic receptor. *Biochem Biophys Res Commun.* 150(2): 665-72, 1988) and **Emorine et al.** (Emorine et al., Molecular characterization of the human beta 3-adrenergic receptor. *Science* 245(4922): 1118-21, 1989), is ***withdrawn*** because the claims have been amended and the amended claim 71 recites the limitation "a first gene product that is a receptor".

5. Previous rejection of claims 71, 72 and 75 under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **Sleckman et al.** (Sleckman et al., Expression and function of CD4 in a murine T-cell hybridoma. *Nature* 328(6128): 351-3, 1987), is ***withdrawn*** because the claims have been amended and the amended claim 71 recites the limitation "a first gene product that is a receptor".

The following 103 rejections are necessitated by claim amendments filed on 01/05/2010.

6. Claims 71 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Capecchi** (Capecchi, Altering the genome by homologous recombination, *Science* 244 (4910):1288-92, 1989) or alternatively, as being over unpatentable over **Thomas et al.** (Site-directed mutagenesis by gene targeting in mouse embryo-derived stem cells, *Cell* 51(3):503-12, 1987) in view of **Petkovich et al.** (Petkovich et al., A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987).

It is noted that **Thomas et al.** (*Cell* 51(3):503-12, 1987; This reference has been cited on page 4 of the IDS filed on 12/13/2006) discloses in the abstract the same teachings as Capecchi (1989) and Figure 1 of Thomas et al. (*Cell* 51(3):503-12, 1987) is the same as Figure 2 of **Capecchi** (1989).

Capecchi (or Thomas et al.) teaches that homologous recombination between DNA sequences residing in the chromosome and newly introduced, cloned DNA sequences (gene targeting) allows the transfer of any modification of the *cloned gene* into the genome of a living cell. Capecchi discusses the status of gene targeting with particular emphasis on germ line modification of the mouse genome, and describes the different methods so far employed to identify those rare embryonic stem cells in which the desired targeting event has occurred (See abstract, Capecchi, 1989). Capecchi (or Thomas et al.) teaches a targeting vector that inserts multiple exons encoding sequence and a neomycin resistant gene (*neo* gene, selected by G418 resistance) into mouse genomic *hprt* locus (See Figure 2(B), shown below, Capecchi, 1989).

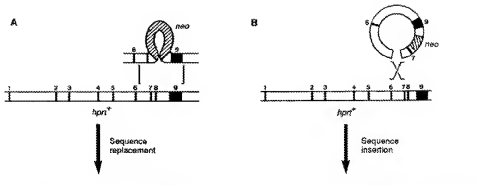

Fig. 2. Disruption of *hprt* by gene targeting with (**A**) a sequence replacement targeting vector or (**B**) a sequence insertion targeting vector. Vectors of both classes contain *hprt* sequences interrupted in the eighth exon with *neo* gene. With the sequence replacement vector, after homologous pairing between the vector and genomic sequences, a recombination event replaces the genomic sequence with vector sequences containing *neo*. Sequence insertion vectors are designed such that the ends of the linearized vector be adjacent to one another on the *hprt* map. Pairing of such a vector with its genome homolog, followed by recombination at the double-strand break, results in insertion of the entire vector into the endogenous gene. This produces a duplication of a portion of *hprt*.

Capecchi et al. (or Thomas et al) does not explicitly teach (i) the first heterologous gene (i.e. a transgene to be knocked-in in a targeted locus in mammalian genome by homologous recombination) product is a receptor, as recited in claim 71, and (ii) wherein the receptor is a retinoic acid receptor, as recited in claim 73 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a retinoic acid receptor was known in the art. For instance, Petkovich et al. disclose a cDNA clone encoding a retinoic acid receptor that binds retinoic acid with high affinity (See abstract, Petkovich et al., 1987).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Capecchi et al. (or Thomas et al.) regarding the targeting vector that inserts multiple exons encoding sequence and a neomycin resistant gene (*neo* gene, selected by G418 resistance) into mouse genomic *hprt* locus, with the teachings of Petkovich et al. regarding a specific cDNA clone encoding retinoic acid receptor, by replacing multiple *hprt* exons sequences taught by Capecchi et al. (or Thomas et al.) with the cDNA clone

encoding a retinoic acid receptor taught by Petkovich et al., to arrive at the claimed DNA construct of claims 71 and 73.

One having ordinary skill in the art would have been motivated to substitute multiple hprt exons sequences taught by Capecchi et al. (or Thomas et al.) with the cDNA clone encoding a retinoic acid receptor taught by Petkovich et al., which is heterologous with respect to the recipient gene *hprt* gene locus, taught by Petkovich et al. in order to drive the expression of a retinoic acid receptor gene bearing any intended modification and targeted it to a designed locus, rather than random integration which cause variations in expression of transgene expression in the genome of recipient cells, in the genome of recipient cells, thereby enabling the functional analysis of the retinoic acid receptor in a consistent genomic setting during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Capecchi (or Thomas et al.) can successfully alter gene of interest in a mammalian genome by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding retinoic acid receptor was readily available by the teachings of Petkovich et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Capecchi** (Capecchi, Altering the genome by homologous recombination, *Science* 244 (4910):1288-92, 1989) or alternatively, as being over unpatentable over **Thomas et al.** (Site-directed mutagenesis by gene targeting in mouse embryo-derived stem cells, *Cell* 51(3):503-12, 1987) in view of

Chernajovsky et al. (Chernajovsky et al., Efficient constitutive production of human fibroblast interferon by hamster cells transformed with the IFN-beta 1 gene fused to an SV40 early promoter. *DNA* 3(4): 297-308, 1984).

The teachings of Capecchi (or Thomas et al.) have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Capecchi (or Thomas et al.) in view of Petkovich et al. (1987).

Capecchi (or Thomas et al.) does not explicitly teach (i) the first heterologous gene (i.e. a transgene to be knocked-in in a targeted locus in mammalian genome by homologous recombination) product is an interferon, as recited in claim 76 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding an interferon was known in the art. For instance, Chernajovsky et al. teach the construction of the plasmid pSVEIF, which harbors the interferon β1 (INF-β1) gene (See Figure 1, Chernajovsky et al., 1984).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Capecchi et al. (or Thomas et al.) regarding the targeting vector that inserts multiple exons encoding sequence and a neomycin resistant gene (*neo* gene, selected by G418 resistance) into mouse genomic *hprt* locus, with the teachings of Chernajovsky et al. regarding a specific cDNA clone encoding interferon β1, by replacing multiple *hprt* exons sequences taught by Capecchi et al. (or Thomas et al.) with the cDNA clone encoding interferon β1 taught by Chernajovsky et al., to arrive at the claimed DNA construct of claim 76.

One having ordinary skill in the art would have been motivated to substitute multiple *hprt* exons sequences taught by Capecchi et al. (or Thomas et al.) with the cDNA clone encoding interferon β1 taught by Chernajovsky et al. in order to drive the expression of interferon β1 gene bearing any intended modification and targeted it to a designed locus, rather than random integration which cause variations in expression of transgene expression in the genome of recipient cells, thereby enabling the functional analysis of the interferon β1 in a consistent genomic setting during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Capecchi (or Thomas et al.) can successfully alter gene of interest in a mammalian genome by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding interferon β1 was readily available by the teachings of Chernajovsky et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

8. Claim 77 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Capecchi** (Capecchi, Altering the genome by homologous recombination, *Science* 244 (4910):1288-92, 1989) or alternatively, as being over unpatentable over **Thomas et al.** (Site-directed mutagenesis by gene targeting in mouse embryo-derived stem cells, *Cell* 51(3):503-12, 1987) in view of **Lindenmaier et al.** (Lindenmaier et al., Isolation of a functional human interleukin 2 gene from a cosmid library by recombination in vivo. *Gene* 39(1): 33-9, 1985).

The teachings of Capecchi (or Thomas et al.) have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Capecchi (or Thomas et al.) in view of Petkovich et al. (1987).

Capecchi (or Thomas et al.) does not explicitly teach (i) the first heterologous gene (i.e. a transgene to be knocked-in in a targeted locus in mammalian genome by homologous recombination) product is an interleukin, as recited in claim 77 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding an interleukin was known in the art. For instance, Lindenmaier et al. teach the construction of the plasmid pAN26-IL2, which harbors the interleukin 2 gene (IL2) (See Figure 1, Lindenmaier et al., 1985).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Capecchi et al. (or Thomas et al.) regarding the targeting vector that inserts multiple exons encoding sequence and a neomycin resistant gene (*neo* gene, selected by G418 resistance) into mouse genomic *hprt* locus, with the teachings of Lindenmaier et al. regarding a specific cDNA clone encoding interleukin 2 gene, by replacing by replacing multiple *hprt* exons sequences taught by Capecchi et al. (or Thomas et al.) with the cDNA clone encoding interleukin 2 taught by Lindenmaier et al., to arrive at the claimed DNA construct of claim 77.

One having ordinary skill in the art would have been motivated to substitute multiple *hprt* exons sequences taught by Capecchi et al. (or Thomas et al.) with the cDNA clone encoding in interleukin 2 gene taught by Lindenmaier et al. in order to drive the expression of interleukin 2 gene bearing any intended modification and targeted it to a designed locus, rather than random

integration which cause variations in expression of transgene expression in the genome of recipient cells, thereby enabling the functional analysis of the interleukin 2 in a consistent genomic setting during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Capecchi (or Thomas et al.) can successfully alter gene of interest in a mammalian genome by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding interleukin 2 gene was readily available by the teachings of Lindenmaier et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

9. Claims 71 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Capecchi** (Capecchi, Altering the genome by homologous recombination, *Science* 244 (4910):1288-92, 1989) or alternatively, as being over unpatentable over **Thomas et al.** (Site-directed mutagenesis by gene targeting in mouse embryo-derived stem cells, *Cell* 51(3):503-12, 1987) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **George et al.** (George et al., Receptor density and cAMP accumulation: analysis in CHO cells exhibiting stable expression of a cDNA that encodes the beta 2-adrenergic receptor. *Biochem Biophys Res Commun.* 150(2): 665-72, 1988) and **Emorine et al.** (Emorine et al., Molecular characterization of the human beta 3-adrenergic receptor. *Science* 245(4922): 1118-21, 1989).

The teachings of Capecchi (or Thomas et al.) and Petkovich et al. 1987 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Capecchi (or Thomas et al.) and Petkovich et al. 1987.

Capecchi (or Thomas et al.) and Petkovich et al. 1987 do not teach the receptor is a 3-β adrenergic receptor, as recited in claim 74 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a 3-β adrenergic receptor was known in the art. For instance, George et al. disclose a plasmid pUC13B2AR containing a beta 2-adrenergic receptor (See Material and Methods, page 666, George et al., 1988) and Emorine et al. teach that human beta 3-adrenergic receptor shares 45.5% identical amino acid sequences of human beta 2-adrenergic receptor.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Capecchi (or Thomas et al.) and Petkovich et al. 1987 regarding the gene targeting construct comprising a retinoic acid receptor inserted in the endogenous genomic copy of the *hprt* gene, with the teachings of George et al. and Emorine et al. regarding a specific cDNA clone encoding a beta 3-adrenergic receptor, by replacing multiple *hprt* exons sequences taught by Capecchi et al. (or Thomas et al.) with the cDNA clone encoding a beta 3-adrenergic receptor taught by George et al. and Emorine et al., to arrive at the claimed DNA construct of claim 74.

One having ordinary skill in the art would have been motivated to combine the teachings of Capecchi et al. (or Thomas et al.) and Petkovich et al. 1987 with the cDNA clone encoding an beta 3-adrenergic receptor taught by George et al. and Emorine et al. in order to drive the expression of beta 3-adrenergic receptor gene bearing any intended modification and targeted it

to a designed locus, rather than random integration which cause variations in expression of transgene expression in the genome of recipient cells, thereby enabling the functional analysis of the beta 3-adrenergic receptor a consistent genomic setting during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Capecchi (or Thomas et al.) and Petkovich et al. 1987 can successfully alter gene of interest in a mammalian genome, including a retinoic acid receptor, by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding a beta 3-adrenergic receptor was readily available by the combined teachings of George et al. and Emorine et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

10. Claims 71, 72 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Capecchi** (Capecchi, Altering the genome by homologous recombination, *Science* 244 (4910):1288-92, 1989) or alternatively, as being over unpatentable over **Thomas et al.** (Site-directed mutagenesis by gene targeting in mouse embryo-derived stem cells, *Cell* 51(3):503-12, 1987) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **Sleckman et al.** (Sleckman et al., Expression and function of CD4 in a murine T-cell hybridoma. *Nature* 328(6128): 351-3, 1987).

The teachings of Capecchi (or Thomas et al.) and Petkovich et al. 1987 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Capecchi (or Thomas et al.) and Petkovich et al. 1987.

Capecchi (or Thomas et al.) and Petkovich et al. 1987 do not teach the receptor is a receptor for infectious agent recited in claim 72, and an HIV receptor recited in claim 75 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a HIV receptor CD4 was known in the art. For instance, Sleckman et al. teach the retroviral vector construction MNST4, which harbors the CD4 gene (the receptor of infectious HIV) (See Figure 1, Sleckman et al., 1987). HIV is an infectious agent (as recited in claim 72) and the CD4 is a cellular receptor of HIV. Through interaction between which HIV envelope protein and CD4 receptor present on cell surface (an HIV receptor as recited in claim 75), the HIV can infect the cell.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Capecchi (or Thomas et al.) and Petkovich et al. 1987, regarding the gene targeting construct comprising a retinoic acid receptor inserted in the endogenous genomic copy of the *hprt* gene, with the teachings of Sleckman et al. regarding a specific cDNA clone encoding HIV receptor, by replacing multiple *hprt* exons sequences taught by Capecchi (or Thomas et al.) with the cDNA clone encoding a HIV receptor taught by Sleckman et al., to arrive at the claimed construct of claims 72 and 75.

One having ordinary skill in the art would have been motivated to combine the teachings of Capecchi (or Thomas et al.) and Petkovich et al. 1987 with the teachings of Sleckman et al. in

order to drive the expression of a HIV receptor gene bearing any intended modification and targeted it to a designed locus, rather than random integration which cause variations in expression of transgene expression in the genome of recipient cells, thereby enabling the functional analysis of the HIV receptor in a consistent genomic setting during pathogenesis of AIDS and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Capecchi (or Thomas et al.) and Petkovich et al. 1987 can successfully alter gene of interest in a mammalian genome, including a retinoic acid receptor, by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding an HIV receptor CD4 was readily available by the teachings of Sleckman et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and ***Response to Applicant's arguments***

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above. It is noted that previous 103 rejections documented on pages 9-24 of the Final office action mailed on 08/05/2009 have been withdrawn. The primary reference, Nandi et al. (Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) cited in the withdrawn 103 rejections, has been replaced with reference Capecchi (Altering the genome by homologous recombination, *Science* 244 (4910):1288-92, 1989) cited in the 103 rejections documented in this office action.

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a

specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Capecchi (or Thomas et al.) with various references pertaining to gene of interest to be knock-in mouse genome have been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

11. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/

Primary Examiner

Art Unit 1632